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MECHANICAL IMPACTS TO THE SKULLS OF RATS PRODUCE SPECIFIC DEFICITS IN MAZE PERFORMANCE AND WEIGHT LOSS: EVIDENCE FOR APOPTOSIS OF CORTICAL NEURONS AND IMPLICATIONS FOR CLINICAL NEUROPSYCHOLOGY[1]

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Summary.—The purpose of this experiment was to induce closed head injuries that might be applicable to clinical neuropsychology. Six adult female albino rats were struck over the right dorsal skull by a 200-gm weight that fell through a 0.9-m tube while another six rats served as controls. The rats that received the impact to the skulls displayed significantly more weight loss and fewer completions of the maze during the subsequent two to four days (effect size about 40%) while their open field behaviors, response latencies to thermal stimulation of the feet, and immobility within a conditioned fear setting did not differ significantly from those of controls. Histological analyses of the brains about 35 days after the impact indicated striking alterations in the morphology of cerebral cortical neurons, strongly suggestive of an apoptotic-like process, within the dorsal cerebral cortices below the likely impact site. Distributions of clusters of these aberrant-looking cells were also evident opposite to the impact site within the ventral cerebrum. Because apoptosis is involved with minimal inflammation and edema, detection of diffuse apoptosis by MRI and CT would be unlikely even though the influence on adaptability would be significant.

During the last 15 years we have assessed more than 500 patients who had sustained significant impacts of mechanical energy to the skull or to the whole body mass. Most of these patients did not display any apparent suspension of consciousness. Frequently their postinjury symptoms would not even be diagnosed as a "concussion" or "mild brain injury" (Elson & Ward, 1994) according to neurologists. Any behaviour developed subsequently to these traumas, especially if more than a few months had elapsed since the injuries, was usually attributed by many general practitioners and neurologists to "psychological" factors.

However, our clinical research has indicated that many of these patients display permanent quantitative deficits that often elude the brief qualitative perspectives of neurological examinations or the superficial observations of many general practitioners (Persinger, 1995a, 1995b). Because the patients can engage in overlearned or procedural responses such as casual conversation or ambulation, these people are considered "normal." On the basis of

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these conclusions some insurance companies attribute the patients' difficulties to "psychological causes" or devious attempts to gain compensation even though there is no evidence that patients are "cured" by a favourable verdict (King, 1997).

We developed a simple technique to simulate in the rat the effects of the types of mechanical impacts that have been sustained by many of our patients who were diagnosed by physicians with the "postconcussional syndrome," "mild brain trauma," or even "compensation neurosis." We realized that some injuries, such as lateral (uncal) transtentorial herniation, associated with the unique features of the human brain's topography (Pang, 1989) would not be accommodated in our approach. Our focus was upon the potential continuum of quantitative diffuse neuronal loss, glial proliferation, or subtle alteration in the function of the blood-brain barrier that might follow a trauma and increase the probability of long-term modification of cerebral function (Cook & Persinger, 1999).

A pilot study with six adult rats indicated that the impact of either a 100-gm or 200-gm weight, dropped through a tube onto the top of the rat's right skull over the cerebrum, produced specific behavioral deficits that might be considered analogous to those reported by human patients. These behaviours included intermittent spatial confusion, difficulty learning new spatial patterns, and protracted losses in body weight without obvious changes in routine behaviours such as ambulation, conditioning to aversive stimuli presented before the injury, or nociceptive thresholds. The present study was designed to replicate and extend these observations.

Method

Subjects

Twelve 9-mo.-old Wistar albino rats were employed as subjects. They had been maintained three per cage within standard wire cages since they had been weaned at approximately 21 days of age. The light:dark cycle had been 12:12, and room temperature had been maintained within 1° of 20°C.

Procedure

After obtaining baseline body weights, all subjects were adjusted to a 23-hr. food deprivation schedule for 10 days until they approached 90% of their free-feed body weights. On any given day each rat was given 30 min. of maze testing followed within a few minutes by 2 min. in the open field and then followed within a few minutes by testing for (thermal) nociceptive threshold. Four hours later, they were tested for fear conditioning.

For three successive days before the treatment each rat was tested singly in a four-arm automated maze. Each arm contained a classical operant lever and a food hopper. The task was to press the lever, obtain the food, leave

the arm, and enter another arm that had not been entered until all the levers at the end of each of the arms had been pressed. Until this criterion occurred, the rat could enter arms repeatedly, but lever pressing would not result in a reward. The numbers of successfully completed trials (all four levers pressed in any order before the next option for obtaining food by lever pressing) within 30 min. were recorded.

For each of the two days before the impact the rats were tested in an open field (Persinger, 1969) for 2 min. after the maze learning. The numbers of squares traversed after 30 sec., 60 sec., and 120 sec. as well as the numbers of fecal boluses, urine episodes, grooming periods, and rearings, were also recorded. For each of the two days before the impact each rat was placed upon a standardized hotplate whose temperature was set at 55°C. The rat was removed after it licked either hind paw twice or 60 sec. had elapsed.

Three days before the treatment the rats were trained for a conditioned fear task. They were placed in a modified operant chamber whose floor grids were electrified. During a 6-min. period an electric shock (0.5 mA, 2-sec.) was delivered after 3, 4, and 5 min. For the next two days the mobility of the rats in the context in which they had received the electric shock was evaluated during an 8-min. period. If the rat was moving or not moving every 8 sec., it was given either a 1 or a 0. The potential score for immobility ranged from 0 to 60.

On the day of the "impact" (after the third day of learning in the maze and after the second day of exposure to the open field, hot plate, and conditioned fear apparatus), each rat was brought singly into the experimental room (not involved with any of the testing). It was held firmly by criss-crossing the forelimbs under the ventral surface and holding this position firmly with the thumb and index finger. This position allowed a secure hold on the rat. The rat's head was then placed on the edge of a Formica-surfaced table so that only the bottom of the head rested firmly on the surface. The rat's body was held by the experimenter's hand in the space beside the table.

The first experimenter held a 0.9-m cardboard tube (from wrapping paper), whose radius was 2 cm, on the top of the rat's head. A 200-gm weight (from an old set of weights used on analytical pan balances) whose diameter was 3 cm and thickness was 3 cm was dropped through the tube. The tube guided the fall of the weight so that the flat surface struck the right top of the rat's skull. Six of the rats, randomly selected, received the impact while the other six rats were held, had the tube placed over their heads, but no weight was dropped. Three of the six rats that received the impact of mechanical energy showed a conspicuous stunned response defined as partial closure of the eyes, a mild whole body shudder, and contralateral contraction of the limbs, whose duration was about 30 sec. None of the rats dis-

played clonic convulsions. After this period the behaviors of these rats were not discriminably different than those of the controls.

The numbers of completed trials in the automated maze were measured for each of the subsequent four days. Open field and fear testing continued for four days after the impact. Body weight was measured every two days for eight days. Thirty-five days after the mechanical impact or the control treatment, the rats were decapitated. After inspection of the superior surface of the skull for indications of injury the brains were removed and fixed in ethanol-formalin-acetic acid. The brains of six of the rats (two controls, two rats that received the mechanical impact and were stunned, and two rats that received the mechanical impact but were not stunned) were processed for histological assessment. Ten micrometer coronal sections were obtained for the area between the caudal parietal lobe and mid-prefrontal lobe and stained with toluidine blue O. Cytomorphology was examined microscopically by each author.

The primary design was a two-way analysis of variance with one between-subject (impact or not) and one within-subject level (days). To accommodate for individual differences relative measures were calculated by dividing the scores for each task on the days after the impact by the mean of the scores for the task during the two days before the impact. *Post hoc* tests were paired *t* tests. All analyses involved SPSS software on a Vax 2000 computer.

Results

Behavioral Data

There were no significant differences (all dfs = 1,10, Fs < 1.00) between the two groups for the pre-injury (baseline) body weight, numbers of squares traversed in the open field, successful completions of the automatic maze, time required to respond to the hot plate, or scores for immobility within a conditioned fear setting. The means and standard deviations for each of these measures were 334 g and 15 gm for body weight, 53 and 22 squares, 29 and 11 successful completions of the maze in 30 min., 17 sec. and 4 sec. for the hotplate latency, and 56 observations and 3 observations of no movement when exposed to the conditioned fear paradigm.

Two-way analysis of variance with one within-subject level (the numbers of successful completions of the maze per session during the baseline and four posttreatment days) and one between-subject level (treatment) indicated that the rats receiving the mechanical impact showed significantly ($F_{1,10}$ = 4.99, $p < .05$; $\eta^2 = .33$) fewer completions of the maze than the control group. However, this main effect was due primarily to an interaction between daily trials and treatment ($F_{4,40} = 3.81$, $p < .05$; $\eta^2 = .28$). *Post hoc* analysis indicated that the interaction was due to the relative decrease in numbers of successful

trials completed per session by the experimental group during the two days following the mechanical impact compared to the control group. The means and standard errors of the mean for the numbers of completions in the maze for the two groups are shown in Table 1.

TABLE 1
MEANS AND STANDARD ERRORS OF MEAN (*SEM*) FOR NUMBERS OF SUCCESSFUL COMPLETIONS OF AN AUTOMATED MAZE WITHIN 30 MIN. PER DAY FOR DAYS BEFORE (–) AND AFTER (+) EITHER MECHANICAL IMPACT OR CONTROL TREATMENT

Preinjury	Controls		Mechanical Impact		η^2 (%)
	M	*SEM*	*M*	*SEM*	
Day –3	2.5	0.6	1.7	0.6	.09
Day –2	8.7	2.9	5.3	1.5	.09
Day –1	10.8	2.4	11.3	2.6	.01
Day +1	15.0	2.7	5.3	4.7	.45
Day +2	17.8	4.2	8.0	2.3	.30
Day +3	15.0	4.3	6.2	1.4	.27
Day +4	15.7	4.2	8.0	1.4	.23

*$p < .05$.

The means and standard errors of the mean for the percentages of successful completions of the automatic maze compared to pretreatment trials are shown in Table 2. Two-way analysis of variance indicated the group that had received the mechanical impact exhibited fewer successful completions of the maze following the injury relative to their performance before the injury ($F_{1,10} = 5.43$, $p < .05$; $\eta^2 = .35$) compared to controls. There was also a statistically significant interaction between treatment and time ($F_{4,40} = 2.74$, $p < .05$; $\eta^2 = .22$) which was in large part responsible for the main differences between days ($F_{4,40} = 2.82$, $p < .05$). *Post hoc* analysis (which used paired *t* tests for each group separately) indicated that the major source of the interaction was due to the significantly poorer learning for the first two days after the injury compared to the subsequent two days displayed by the group that received the mechanical impact.

Two-way analysis of variance for the absolute body weights during the pre- and postinjury periods showed no statistically significant difference between the conditions ($F_{1,10} = .30$, $p > .05$). There was a statistically significant interaction between days and the conditions ($F_{4,40} = 3.51$, $p < .01$; partial $\eta^2 = 26\%$). *Post hoc* analysis indicated the interaction was due to the loss of body weight during the eight days after the injury by the group that received the mechanical impact compared to the controls.

The means and the standard errors of the mean for the percentage changes in body weights for the group that received the mechanical impact compared to the reference group are shown in Table 2. Two-way analysis of

TABLE 2
MEANS AND STANDARD ERRORS OF MEAN (*SEM*) FOR PERCENTAGE CHANGES IN BODY WEIGHT AND NUMBERS OF SUCCESSFUL COMPLETIONS OF THE MAZE COMPARED TO BASELINE VALUES FOR CONTROL GROUP AND GROUP RECEIVING MECHANICAL IMPACT

Postinjury Time	Controls		Mechanical Impact	
	M	*SEM*	*M*	*SEM*
Change in Number of Maze Completions, %				
Day 1	69	27	–39	28
Day 2	77	28	–21	28
Day 3	33	25	–19	27
Day 4	48	28	–13	26
Change in Body Weight, %				
Day 2	–2.0	1.1	–5.8	1.1
Day 4	–2.2	2.0	–7.5	1.9
Day 6	0.0	1.1	–6.6	1.8
Day 8	–2.3	.8	–8.3	1.6

*$p < .05$.

variance with one between-subject level (treatment) and one within-subject level (repeated measures) showed that the group that received the mechanical impacts lost significantly more body weight relative to their individual baselines ($F_{1,10} = 7.29$, $p < .05$; $\eta^2 = .42$) compared to the control group. Neither the repeated measure ($F_{3,30} = 1.67$, $p > .05$) nor the interaction between treatment and time after the injury ($F_{3,30} = .65$, $p > .05$) were significant statistically.

The two-way analyses of variance for the percentage changes in numbers of squares traversed in the open field, latency to respond to nociceptive stimuli, and numbers of episodes when the rat was not moving ("freezing") within a conditioned fear context showed no statistically significant differences between the treatments (all $Fs < 1.0$). The interactions between treatments and days were also not significant statistically (all $Fs > 1.0$). However, there were statistically significant changes (all $Fs > 10.00$, $p < .001$) over time for the absolute ($dfs = 6,60$) and relative ($dfs = 4,40$) measures for freezing (less), ambulation (less), and latencies to respond to the hotplate (quicker).

An exploratory discriminant analysis was completed to discern whether magnitude of the differences between the groups could correctly classify the individuals within each group. To simulate the procedures for a clinical neuropsychological assessment, we calculated the mean score for the numbers of squares traversed, groomings, boluses, rearings, and maze completions, the latencies to be removed from the hotplate, and the numbers of episodes of immobility for the three days after the treatment for the controls only. The mean and standard deviation for each of the means for each task for the control group were then employed to calculate z scores for each rat from the control and treatment groups. This procedure might be analogous to com-

paring all of the z scores for the neuropsychological tests of a given patient to reveal "relative" weaknesses and strengths.

Because only 12 rats were involved the numbers of variables that could enter the function were restricted to two. The two variables entered were the z scores for the numbers of maze completions and the numbers of freezing responses. The function [canonical correlation $(df=2)=.79$, $p<.01$] correctly classified 92% of the rats. One of the rats that received the mechanical impact was classified in the normal (control) group. The means for the z scores for the maze and conditioned fear scores were −1.6 and −.6, respectively, for the group that received the head trauma.

Histology.—All six of the rats that received the mechanical impacts displayed discolorations within the periosteum over the right central skull. These discolorations were about 1-mm to 3-mm in diameter, about 5-mm lateral to the longitudinal suture, with their outer edges adjacent to the parasagittal ridge. They were located over the parietal bone. The results of the histological examinations showed no conspicuous neuronal or glial anomalies

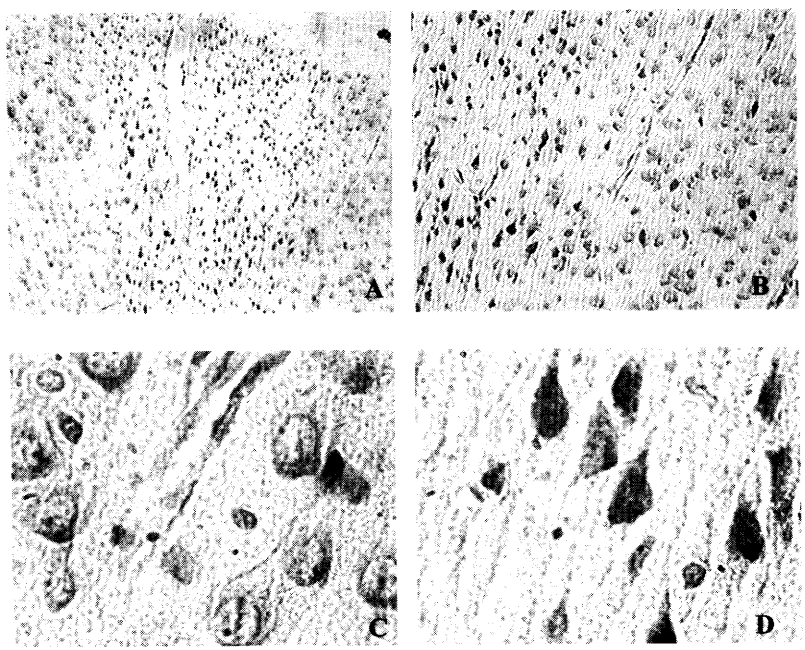

FIG. 1. Photomicrographs of the parietal cortices of a rat that sustained an impact of mechanical energy over the right hemisphere. A: 40x shows the wedge-shaped area of darkened, shrunken neuronal soma 35 days after impact. B: 100x shows the smaller soma on the left and the normal larger soma on the right. C: 1000x contains normal neurons showing typical nuclei and nucleoli. D: 1000x illustrates reduction in size of soma and evidence of disruption of nuclear chromatin material.

within the cerebral cortices of either hemisphere for the control rats. Three of the four rats that had received the mechanical impacts exhibited evidence of circumscribed neuronal anomalies within the cortices of the right hemisphere. Discontinuities within the extracellular matrix, typical of malacia, within these regions were evident. Gliosis was not observed.

An example of a circumscribed anomaly within the cerebral cortices of the right parietal cortices (parietal association cortex) of Rat 1304 that exhibited "stunned behavior" following the impact is shown in Fig. 1. This rat's z score for the maze performance was below normal (z score <-2.00). The medial edge of the strip is about 1 mm lateral to the longitudinal sulcus. The majority of neurons within the wedged area, approximately 600 micrometers wide within the upper cortical layers and 300 micrometers wide within the deepest layers, were smaller by about 50% than the neighbouring normal neurons. The "shrunken" neuronal somas also exhibited markedly

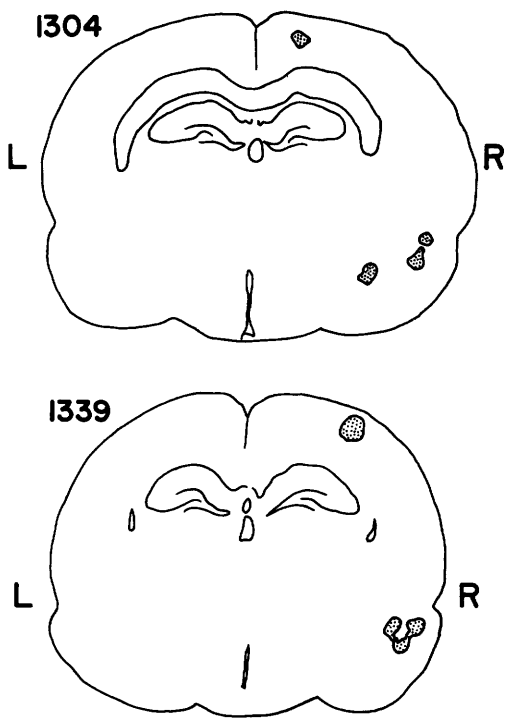

FIG. 2. Drawn outlines of coronal sections of two rats that sustained a mechanical impact over the right (R) cerebral hemisphere. The areas of neuronal anomalies beneath the impact sites and deep within the cerebrum within limbic structures are indicated. There were no anomalies in the left hemispheres of these rats.

reduced widths for their nuclei. The staining patterns of the nuclei and nucleoli were typical of disruption or dispersion of chromatin material.

Several focal areas of anomalous cells, similar in morphology to those beneath the impact sites, were noted along the opposite boundaries of the cerebrum. They were lateralized from the midline. As shown in Fig. 2, for Rats 1304 and 1339, circumscribed areas of anomalous cells were noted within the endopiriform cortices, perirhinal cortices and the basolateral amygdala. The specific areas differed slightly for each rat.

The z scores (ranging from –0.05 to –2.9) for the four rats that had received the mechanical impact and for which we had the histological data were correlated with the numbers of discernable anomalies noted in the cortices of the right hemisphere. Each of four slides for each brain had been evaluated for morphological anomalies. The correlation coefficients (*rho* and r, respectively) between the maze performance z scores and the numbers of anomalies were –.95 and –.96 ($p < .05$), respectively.

Discussion

We (Baker-Price & Persinger, 1996) have been pursuing novel treatments that might facilitate a human's adaptation following impacts of mechanical energies to the brain when these traumas were not sufficient to induce unconsciousness or to result in a Glasgow Coma Score of less than about 13. Such patients usually do not display neurological symptoms by the time paramedics arrive and later do not display any gross neurological deficits. These patients appear to be able to engage in well learned procedural tasks. Their major difficulties involve learning new, very complex material (Persinger, 1995a, 1995b) and the increased incidence of complex partial epileptic-like symptoms. Their manifestations are often attributed to "enhanced distractibility," "diminished motivation," or "increased fatigue."

In the present study the consequences of an impact of mechanical energy delivered by dropping a 200-gm weight from 0.9 m resulted in a transient disruption of the rats' behavior. Some rats displayed contralateral contraction of the limbs and immobility. However, within about 30 sec., they were engaging in normal rat behavior such as sniffing and ambulation over the table's surface. Except for mild "stunning," many humans who sustain similar impacts show "normal" behavior. However, these people frequently develop complications and difficulties with adaptation during subsequent weeks to months.

The results of this study indicated that a single impact of mechanical energy to the right dorsal skull of rats was sufficient to affect learning of a spatial maze adversely for at least two subsequent days. A significant loss of body weight, that emerged most conspicuously about four to six days after the injury, was also measured. The data in Tables 1 and 2 indicated that the

control rats, that had received the identical treatment except a weight was not dropped on the skull, continued to learn the maze. The effect was sufficient to affect the group average and to override individual differences.

When each individual was employed as its own control, an option usually not possible for clinical neuropsychological assessments, the group of rats that received the mechanical impacts showed 20% to 40% decreases in the numbers of trials completed during the 30 min. of maze learning compared to the baseline period. The rats that received the mechanical impact did not progress beyond their performance before the injury. That the deficits were not due to a generalized reduction in ambulation was indicated by the absence of a significant difference in open field activity between the treated and control groups.

These results suggest the mechanical impact may have interfered with the rats' ability to continue learning a new task. In our previous unpublished studies rats that had been exposed to this maze for about 10 successive days and had approached asymptote with respect to the number of trials per day did *not* show any significant changes in performance during the days following the same type of mechanical injury. This difference would be consistent with our working hypothesis, derived from clinical observations, that impacts of small mechanical energies interfere with the performance of more complex tasks that require new learning or are in the process of being acquired.

The effects of the mechanical impacts were specific to learning a complex task. The rats that had received the single mechanical impact did not show any changes in their conditioned fear response to a context to which they had been exposed before the injury. In addition, their general sensitivity to painful stimuli, as inferred by the latency of response when placed on a hotplate, did not differ significantly after the injury relative to that of the control group.

Like human populations, there was obvious individual variability in the severity of the deficits for the rats that received the "same" impact. Two of the three rats that showed "stunning" and transient contralateral limb tonus had z scores of lower than –2.0 (below normal) for their maze performance. However, one of the rats that was struck by the weight and did not exhibit this "immediate" obvious clinical manifestation also showed a below normal score. She also demonstrated focal, anomalous neuronal soma over the likely impact site.

The presence of several circumscribed areas of anomalous neuronal soma deep within the brain would be consistent with the consequences of "counter coup" forces. As shown in Fig. 2, these areas within the limbic region were discrete and similar in cross-sectional area to those beneath the

impact site. However, the integrated diameters of these regions were larger. The absence of apparent neuronal anomalies between the dorsal and ventral foci suggests the mechanical forces were propagated through brain matter from the impact site without translation into kinetic components that affect the cell's physiology.

We did not observe spontaneous limbic seizures in these rats. However, it is possible their brains would now be more vulnerable to kindling. Rats in which brain damage has been induced by systemic injection of lithium (3 mEq/kg) and the muscarinic agent pilocarpine (30 mg/kg) develop spontaneous seizures between 10 days to 50 days after the initial status epilepticus (Persinger & Chellew-Belanger, 2001). This latency suggests that specific types of brain injury may facilitate intermittent volleys of stimulation that ultimately kindle the rat brain to display its most common form of partial complex (limbic motor) seizures manifested as rearing, rapid forelimb clonus, and falling. In the gyrencephalic human brain these overt behaviours are less common. The processes are more often displayed as transient electroencephalographic anomalies and symptoms typical of an epileptic spectrum disorder.

The histological analyses suggested that the forces associated with the mechanical impact produced circumscribed disruptions within the cerebral cortices. The morphological characteristics of the neurons were consistent with but not definitive for apoptosis (Kerr, 2002). The neurons within the area under the impact site were about 50% smaller than adjacent neurons or neurons within the same space in the other hemisphere. The nuclei were smaller and showed patterns of basophilic staining suggestive of condensed nuclear chromatin.

Apoptosis is considered a programmed cell death (Alberts, Johnson, Lewis, Raff, Roberts, & Walter, 2002) and results in cell loss without the inflammation and subsequent edema that follows classical necrosis when the cell membrane is severely compromised. This slower process, which may subserve a general homeostatic function, is mediated by a cascade of different caspases via either activation of receptors expressed on the surface of the neuron or through release of apoptosis-activating factors from the mitochondria (Thornberry & Lazebnik, 1998). This slow death or "shrinkage necrosis" (Kerr, 2002) allows the system to remain homeostatic.

On the other hand, protracted anoxia or ischemia results in necrosis whereby cytoplasmic constituents are extruded into extracellular space. Traditional models to study brain injury have involved fluid percussion (Hayes, Lyeth, & Jenkins, 1989), occlusion of an artery by ligation (Henshall, Skradski, Meller, Araki, Minami, Schindler, Lan, Bonislawski, & Simon, 2002), or the induction of excitotoxic seizures (Persinger, Bureau, & Peredery, 1994;

Henshall, *et al.*, 2002). All of these insults primarily produce necrosis and the neurochemical and cytological consequences that result in inflammation and edema. As emphasized by Gennarelli (1994), several models, including damage from mechanical impacts, may be required to approximate human head injury.

If apoptosis, particularly a much delayed form, slowly emerges following the propagation of mechanical energy into the brain, then the neurons would slowly shrink. Because both Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT) detect the types of changes within brain space typically associated with altered water content or neuronal density, these methods would not reveal anomalies. Even at the most optimal resolutions (about 1 mm) available to date, the cortices might appear normal.

However, the necessary regression of the more distal dendrites because of the shrinkage of the soma and the compromised metabolic capacity of the cytoplasmic machinery, particularly for protein synthesis, would limit the brain's processing capacity. The attenuated potential for replacing or forming new dendritic spines could simulate earlier aging. It may be relevant that caspase-6 has a significant role in neuronal apoptosis and is involved with processing of amyloidal precursor protein in the brains of Alzheimer's patients (Pellegrini, Passer, Tabaton, Ganjei, & D'Adamio, 1999). At least two studies have suggested that patients with head injuries may display an earlier onset of presenile dementias (Gedye, Beattie, Tuokko, Horton, & Korsarek, 1989; Graves, White, Koepsell, Reifler, van Belle, Larson, & Raskind, 1990).

For human beings, behavioral consequence would be very similar to accelerated aging whereby the person would no longer be able to adapt quickly to changing, complex environments. If this type of neuronal shrinkage required several weeks to months to complete, then endocrine factors, particularly the adrenocorticotrophic hormone-cortisol pathway (Kerr, 2002) might modulate the severity of the neuronal response. If this response was more diffuse through large volumes of the cerebrum, there would be no obvious enlargements of ventricles or sulci, such as occurs in severe neuronal necrosis (Bigler, Kurth, Blatter, & Abildskov, 1992). The person might fatigue quickly and easily and show permanent mild to moderate neuropsychological impairments despite a "normal" CT scan or MRI.

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